Iskedjian M, Bereza B et al. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin 2007;23(1):17-24.

Design: Meta-analysis of clinical trials

PICOS:

- **P**atients: Adults with MS or comparable neuropathic pain
- **I**nterventions: Cannabis-based drugs at any dose and route of administration, with any duration of administration
- **C**omparison: Placebo, another active drug, or the same drug at a different dose, dosage form, or route of administration
- **O**utcome: Pain scores on a 10 cm VAS or comparable scale
- **S**tudies: Randomized, double-blind, peer-reviewed published articles (not abstracts from professional meetings)

Study search and selection:

- MEDLINE, EMBASE, Cochrane, and HealthSTAR databases from inception through June 2006
- Keywords: nabilone, dronabinol, cannabis, cannabinoid AND neuropathic pain, multiple sclerosis
- Two authors independently rated articles for quality using the 5 point Jadad scale (based on randomization, blinding, and accounting for withdrawals)
- 6 articles were selected following the search, and 1 additional article was supplied by the manufacturer of the drug
- Cannabidiol/THC buccal spray, cannabidiol, and dronabinol were compared with placebo, and the resulting meta-analysis had non-significant homogeneity, with I^2 values of 0, meaning that the studies were combinable as cannabis trials
- Publication bias did not appear to be present
- A random effects meta-analysis comparing cannabis drugs and placebo showed no significant difference between baseline and follow-up for placebo groups; in contrast, the cannabis preparations produced baseline-endpoint pain reductions of 1.6 points on an 11 point scale, showing superiority of cannabis preparations to placebo
- Adverse events led to nearly identical withdrawal rates for cannabis (5.5%) and placebo (5.1%); dizziness was reported by 35% of cannabis patients and by 10.1% of placebo patients

Authors' conclusions:

- Cannabinoid drugs are associated with a clinically relevant reduction in pain scores in neuropathic pain patients
- This conclusion depends on an assumption that MS pain and other neuropathic pains respond similarly to cannabinoids

- There may be some discussion about the relevant effect size for pain reduction on the 11 point scale generally used in pain studies; whether one uses 2 points or 1.5 points, cannabinoids would be more effective than placebo
- Some patients, due to inherent differences in cannabinoid receptors in the brain, may be cannabinoid non-responders, while others are responders
- It would follow that cannabinoids are highly effective in some patients and ineffective in others; when these patients are studied together, the resulting estimate of effect size would tend to be conservative
- A need exists for further studies of cannabinoids in patients with MS

Comments:

- The number of studies is fewer than the number of "trials," due to some articles having more than one comparison; it appears that these were analyzed as separate trials
- Publication bias was not detected, but with the number of studies available, funnel plots and significance tests for publication bias are likely to be underpowered
- The summary of efficacy in Table 2 is probably based on a forest plot which is not presented; the absence of such a plot leaves it unclear which studies are being combined, and which effects are being measured
- The studies were not significantly heterogeneous, and either a fixed effect or random effects model can be used
- The choice of a random effects model was made because "it allows for more weight to be given to larger studies"
- This is very unclear; if it means that larger studies have more weight than smaller studies, this is true for both fixed effect and random effects models; making the stated choice meaningless
- If the comparison "more weight" for larger studies means that a random effects model gives more relative weight to larger studies than smaller studies than a fixed effect model gives, the statement is incorrect: random effects models give relatively more weight to smaller studies than do fixed effect models
- Some of the included studies were crossover trials; since there is more than one method of combining data from these studies into a meta-analysis, it would be desirable to discuss which method was used and how potential problems with unit-of-analysis errors were handled (standard errors are likely to be too large); there is no discussion of this issue
- One of the studies in Table 1 identified as "cannabidiol" is Karst 2003; this was not a study of cannabidiol, but of a carboxylic acid derivative of THC, namely CT-3 or ajulemic acid
- Two of the references (#40, Bosworth and #41 Dempster) are unpublished and not available (neither protocol number on the GW Pharma website yields any data)

Assessment: Inadequate for evidence about cannabinoids for neuropathic pain (method of combining studies cannot be reproduced; incorrect assumptions about the consequences of random effects models on large vs. small studies)